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PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Michael R. Slater *et al.*
Serial No.: 09/641,319 Group No.:
Filed: 08/18/00 Examiner:
Entitled: **Mutant TNE Polymerases**

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Assistant Commissioner for Patents
Washington, D.C. 20231

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Sir or Madam:

Enclosed please find an Information Disclosure Statement and Form PTO-1449, including copies of the references contained thereon, for filing in the U.S. Patent and Trademark Office.

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Dated: April 11, 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Michael R. Slater *et al.*
Serial No.: 09/385,986 Group No.:
Filed: 08/30/99 Examiner:
Entitled: **THERMOPHILIC DNA POLYMERASES FROM THERMOTOGA NEAPOLITANA**

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 CFR § 1.8(a)(1)(i)(A)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on April 11, 2001.

By: Mary Ellen Waite
Mary Ellen Waite

Sir or Madam:

The present application is a Continuation of copending application(s) 09/385,986 filed on 08/30/99 which is a continuation of U.S. Patent Application Serial No. 08/484,661 now U.S. Patent No. 6,001,645 issued December 14, 1999.

The citations listed below, copies attached, may be material to the examination of the above-identified application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The Examiner is requested to make these citations of official record in this application.

The following printed publications are referred to in the body of the specification:

- U.S. Patent No. 4,889,818, issued December 26, 1989 to Gelfand *et al.*;
- U.S. Patent No. 5,352,600, issued October 4, 1994 to Gelfand *et al.*;
- U.S. Patent No. 5,079,352, issued January 7, 1992 to Gelfand *et al.*;
- U.S. Patent No. 5,210,036, issued May 11, 1993 to Comb *et al.*;
- U.S. Patent No. 5,322,785, issued June 21, 1994 to Comb *et al.*;
- U.S. Patent No. 4,683,195, issued July 28, 1987 to Mullis *et al.*;
- U.S. Patent No. 4,683,202, issued June 28, 1987 to Mullis;

- U.S. Patent No. 4,965,188, issued October 23, 1990 to Mullis *et al.*;
- U.S. Patent No. 5,322,770, issued June 21, 1994 to Gelfand;
- U.S. Patent No. 5,075,216, issued December 24, 1991 to Innis *et al.*;
- U.S. Patent No. 5,324,637, issued June 28, 1994 to Thompson *et al.*;
- European Patent Pub. No. 258,017 of Erlich *et al.*, published March 2, 1988;
- PCT Pub. No. WO 94/26766 of Barnes, published November 24, 1994;
- PCT Pub. No. WO 92/06188 of Barnes *et al.*, published April 16, 1992;
- PCT Pub. No. WO 89/06691 of Gelfand *et al.*, published July 27, 1989;
- PCT Pub. No. WO 92/03556 of Gelfand *et al.*, published March 5, 1992;
- PCT Pub. No. 92/06200 of Gelfand *et al.*, published April 16, 1992;
- PCT Pub. No. WO 91/09950 of Gelfand *et al.*, published July 11, 1991;
- PCT Pub. No. WO 91/09944 of Gelfand *et al.*, published July 11, 1991;
- PCT Pub. No. WO 92/09689 of Mathur, published June 11, 1992;
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- Jannasch *et al.*, "Validation of the Publication of New Names and New Combinations Previously Effectively Published Outside the IJSB," *Int. J. Syst. Bacteriol.*, 39:93 (1989);

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- Frey and Suppmann, "Demonstration of the Expand™ PCR System's Greater Fidelity and Higher Yields with a *lac*I-based PCR Fidelity Assay," *Biochemica* 2:8 (1995);
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- Provost *et al.* "Transgenic Systems for *In Vivo* Mutation Analysis," *Mut. Research* 288:133 (1993).

The following patents and printed publications were not referred to in the body of the specification but are cited in U.S. Patent No. 6,001,645 issued December 14, 1999, which is the parent of this application, and may be material to the examination of the instant application.

- PCT Pub. No. WO 96/10640 to Hughes *et al.*;
- Simpson *et al,* "Purification of a Thermostable DNA Polymerase from a *Thermotoga* Species," Annals of New York Academy of Sciences 613:426-428 (1990);
- U.S. Patent No. 5,498,523 to Tabor *et al.*;
- European Patent Pub. No. 655,506 to Tabor *et al.*;
- Tabor *et al.*, "A single residue in DNA polymerases of the *Escherichia coli* DNA polymerase I family is critical for distinguishing between deoxy and dideoxyribonucleotides," Proc. Natl. Acad. Sci 92:6339-6343 (1995);
- PCT Pub. No. WO 94/05797 to Kiselev *et al.*;
- U.S. Patent No. 5,455,170 to Abramson *et al.*;
- PCT Pub. No. WO 93/25706 to Buchardt *et al.*;
- European Patent Pub. No. 371,437 to Soderland *et al.*;

- U.S. Patent No. 5,491,086 to Gelfand *et al.*;
- Canadian Patent Application No. 2,127,188 to Gelfand *et al.*;
- U.S. Patent No. 5,466,591 to Abramson *et al.*;
- U.S. Patent No. 5,420,029 to Gelfand *et al.*;
- U.S. Patent No. 5,374,553 to Gelfand *et al.*;
- U.S. Patent No. 5,338,671 to Scalice *et al.*;
- U.S. Patent No. 5,409,811 to Tabor *et al.*;
- U.S. Patent No. 5,405,774 to Abramson *et al.*;
- PCT Pub. No. 92/06202 to Gelfand *et al.*;
- U.S. Patent No. 4,962,020 to Tabor *et al.*;
- Reeve *et al.*, "A novel thermostable polymerase for DNA sequencing," Nature, 376:796-797 (1995);
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- Barnes, "PCR amplification of up to 35-kb DNA with high fidelity and high yield from λ bacteriophage templates," Proc. Natl. Acad. Sci. 91:2216-2220 (1994); and
- Windberger *et al.*, Arch. Microbiol. 151:506-512 (1989).

Applicants have become aware of the following printed publications which are not prior art:

- U.S. Patent 6,077,664;
- U.S. Patent 5,980,890;
- U.S. Patent 5,861,295;
- Slater, M.R. *et al.*, "DNA Polymerase I of Thermus neapolitane (Tne) and Mutant Derivatives," (Abstract) Seventh International Genome Sequencing and Analysis Conference, Sep. 1995; and
- Schlesinger *et al.*, "Inclusion of OmniBase Enzyme mix in reaction cocktails facilitates sequencing templates with strong secondary structure," (Abstract) The Fidelity of DNA replication, Wrightsville Beach, Sept 10-15, 1995.

The Applicants have copied claims from U.S. Patent Nos. 5,912,155 and 5,939,301 in order to preserve the right to provoke an interference proceeding. The following patents are related to or are said patents:

- U.S.Patent 5,939,301 to Hughes, Jr. *et al.*;
- U.S. Patent 5,912,155 to Chatterjee *et al.*;
- U.S. Patent 5,948,614 to Chatterjee;
- U.S. Patent 6,015,668 to Hughes *et al.*;

Applicants have become aware of the following printed publications which may be material to the examination of this application:

- U.S. Patent 5,614,365 to Tabor *et al.* describes a modified gene encoding a modified DNA polymerase that is better able than the naturally occurring polymerase to incorporates dideoxy-nucleotides instead of the corresponding deoxynucleotide. This Patent does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- U.S. Patent 5,624,833 to Gelfand *et al.* describes a purified thermostable enzyme from the eubacterium *Thermotoga maritima*. This Patent does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;

- U.S. Patent 5,047,342 to Chatterjee describes a recombinant DNA molecule having a structural gene encoding a processive, thioredoxin-independent DNA polymerase, a promoter, and an origin of replication. This Patent does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- U.S. Patent 5,173,411 to Tabor *et al.* describes a method for determining the nucleotide base sequence of a DNA molecule. This Patent does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- U.S. Patent 5,270,170 to Schatz *et al.* describes a random peptide library constructed by transforming host cells with a collection of recombinant vectors that encode a fusion protein comprised of a DNA binding protein and a random peptide and also encode a binding site for the DNA binding protein can be used to screen for novel ligands. This Patent does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- U.S. Patent 5,270,179 to Chatterjee describes a recombinant DNA molecule having a full length or truncated T5 DNA polymerase structural gene, each encoding a processive, thioredoxin-independent DNA polymerase. This Patent does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- EP Patent 351.138 describes methods for DNA sequencing. This Patent does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- EP Patent 386,859 describes modified DNA polymerases suitable for DNA sequencing and methods of producing the polymerases. This Patent does not describe a composition comprising a purified DNA polymerase, or fragments

thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;

- EP publication 516,245 describes methods of DNA sequencing. This Publication does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- PCT Publication WO 90/08839 describes a nucleotide sequencing reaction concentrate comprising a thermostable polymerase. This Publication does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- PCT Publication WO 91/02090 describes a modified Taq polymerase, its manufacture, and its method for use. This Publication does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- PCT Publication WO 91/16446 describes an improved method for determining the nucleotide base sequence of a DNA molecule. This Publication does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- PCT Publication WO 93/02212 describes a method for the amplification and sequencing of DNA or RNA. This Publication does not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Jannasch *et al.*, "*Thermotoga neapolitana* sp. nov. of the Extremely Thermophilic, Eubacterial Genus *Thermotoga*," Archives of Microbiology 150(1):103-104 (1988) describes a second species of the extremely thermophilic, eubacterial genus *Thermotogas* (*Thermotoga neapolitana*) clearly distinguished from the type species *Thermotoga maritima* by physiological and phylogenic criteria. Jannasch *et al.* do not describe a composition comprising a

purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;

- Astatke, M. *et al.*, "Deoxynucleoside Triphosphate and Pyrophosphate Binding Site in the Catalytically Competent Ternary Complex for the Polymerase Reaction Catalyzed by DNA Polymerase I (Klenow Fragment)," J. Biol. Chem. 270(4):1945-1954 (Jan. 1995) describes the use of site-directed mutagenesis to identify those amino acids residues that interact with the deoxynucleoside triphosphate and pyrophosphate in the Klenow fragment-DNA-dNTP ternary complex. Astatke, M. *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Basu, A. and Modak, M.J., "Identification and Amino Acid Sequence of the Deoxynucleoside Triphosphate Binding Site in *Escherichia coli* DNA Polymerase I," Biochemistry 26:1704-1709 (1987) describes the inactivation of E. coli polymerase I by the covalent attachment of pyridoxal phosphate. Basu and Modak do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Beese, L.S. *et al.*, "Crystal Structures of the Klenow Fragment of DNA Polymerase I Complexed with Deoxynucleosides Triphosphate and Pyrophosphate," Biochemistry 32:14095-14101 (1993) describes crystal structures of the Klenow fragment of DNA polymerase I complexed with dNTPs or pyrophosphate. Beese *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Blanco, L. *et al.*, "Evidence favouring the hypothesis of a conserved 3'-5' exonuclease active site in DNA-dependent DNA polymerases," Gene 112:139-144 (1992) describes amino acid alignments of the N-terminal domain of 33 DNA-dependent DNA polymerases encompassing the putative segments ExoI, ExoII and ExoIII. The alignments were used to identify and/or correct some of the most conserved segments in certain DNA polymerases. Blanco *et*

al. do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*; ;

- Braithwaite, D.K. and Ito, J., "Compilation, alignment, and phylogenetic relationships of DNA polymerases," Nucleic Acids Res. 21(4):787-802 (1993) describes alignments of DNA polymerase sequences to facilitate the identification of conserved and viable regions of the DNA polymerase. Braithwaite and Ito do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Carroll, S.S. *et al.*, "A Mutant of DNA Polymerase I (Klenow Fragment) with Reduced Fidelity," Biochemistry 30:804-813 (1991) describes an investigation of the kinetic parameters governing incorporation of correct and incorrect bases into synthetic DNA duplexes by Klenow fragment and two Klenow fragments mutants. Carroll *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Das, S.K. and Fujimura, R.K., "Processiveness of DNA Polymerases: A Comparative Study Using a Simple Procedure," J. Biol. Chem. 254(4):1227-1232 (1979) describe a procedure for analyzing the processivenes of DNA polymerases. Das and Fujimura do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Delarue, M. *et al.*, "An attempt to unify the structure of polymerases," Prot. Engin. 3(6):461-467 (1990) describes the alignment of the bacteriophage SPO2 polymerase with 5 other polymerase sequences in order to narrow the conserved motifs of the polymerases. Delarue *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;

- Donlin, M.J. and Johnson, K.A., "Mutants Affecting Nucleotide Recognition by T7 DNA Polymerase," Biochemistry 33:14908-14917 (Dec. 1994) describes two mutations of the DNA polymerase from bacteriophage T7 that effect nucleotide selection. Donlin and Johnson do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Dunn, J.J. and Studier, F.W., "Complete Nucleotide Sequence of Bacteriophage T7 DNA and the Locations of the T7 Genetic Elements," J. Mol. Biol. 166:477-535 (1983) describes the complete nucleotide sequence of bacteriophage T7 DNA. Dunn and Studier do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Freemont, P.S. *et al.*, "A Domain of the Klenow Fragment of Escherichia coli DNA Polymerase I Had Polymerase but No Exonuclease Activity," Proteins: Struct. Funct. Genet. 1:66-73 (1986) describes the crystal structure of the Klenow fragment of *E. coli* polymerase I. The crystal structure revealed two domains, one for dNTP binding and the other DNA binding. Freemont *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Fujimura, R.K. and Roop, B.C., "Characterization of DNA Polymerase Induced by Bacteriophage T5 with DNA Containing Single Stranded Breaks," J. Biol. Chem. 251(7):2168-2175 (1976) describes the purification and characterization of DNA polymerase induced by bacteriophage T5. Fujimura and Roop do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Fujimura, R.K. *et al.*, "Physical Locus of the DNA Polymerase Gene and Genetic Maps of Bacteriophage T5 Mutants," J. Virology 53(2):495-500 (1985) describes the identification of the physical locus of the DNA polymerase gene of bacteriophage T5 by the transformation of *E. coli* with DNA segments

encoding the gene. Fujimura *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;

- Gutman, P.D. and Minton, K.W., "Conserved sites in the 5'-3' exonuclease domain of *Escherichia coli* DNA polymerase," Nucleic Acids Res. 21(18):4406-4407 (1993) describe comparison of the *E. coli* Pol I N-terminal regions with three bacterial PolI-like enzymes, allowing for the identification of conserved regions. Gutman and Minton do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Ito, J. and Braithwaite, D.K., "Compilation and alignment of DNA polymerase sequences," Nucleic Acids Res. 19(15):4045-4057 (1991) describe the alignment of the amino acid sequences of DNA polymerases and the classification of DNA polymerases into families A, B, and C. Ito and Braithwaite do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Joyce, C.M. *et al.*, "Nucleotide Sequence of the Escherichia coli polA Gene and Primary Structure of DNA Polymerase I," J. Biol. Chem. 257(4):1958-1964 (1982) describe the nucleotide sequence of a 3.2 kb region of the *E. coli* polA gene, comprising the coding region for DNA polymerase I. Joyce *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Joyce, C.M., "Can DNA polymerase I (Klenow Fragment) serve as a model for other polymerases?" Curr. Opin. Struct. Biol. 1(1):123-129 (1991) reviews recent alignments of the sequences of a large number of polymerases in order to investigate the suitability of Klenow fragment as a model for other polymerases. Joyce *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;

- Joyce, C.M. and Steitz, T.A., "Function and Structure Relationships in DNA Polymerases," Annu. Rev. Biochem. 63:777-822 (Jul. 1994) review function and structure of DNA polymerases. Joyce and Stietz do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Leavitt, M.C. *et al.*, "T5 DNA polymerase: Structural-functional relationships to other DNA polymerases," Proc. Natl. Acad. Sci. USA 86:4465-4469 (1989) describe alignments of T5 DNA polymerase with a large group of DNA polymerases. Leavitt *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Ollis, D.L. *et al.*, "Structure of Large fragment of *Escherichia coli* DNA polymerase I complexed with dTMP," Nature 313:762-766 (1985) describe the crystal structure of the large proteolytic fragment of *E. coli* DNA polymerase I complexed with deoxythymidine monophosphate. Ollis *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Pandey, V.N. *et al.*, "Role of Lysine 758 of Escherichia coli DNA Polymerase I as Assessed by Site-directed Mutagenesis," J. Biol. Chem. 269(18):13259-13265 (May 1994) describe investigation of the role of K758 of E. coli DNA polymerase I in the catalytic mechanism. Pandey *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Pelletier, H. *et al.*, "Structures of Ternary Complexes of Rat DNA Polymerase β, a DNA Template-Primer, and ddCTP," Science 264:1891-1903 (Jun. 1994) describe the crystal structure of ternary complexes between rat DNA polymerase β, DNA template-primer, and ddCTP. Pelletier *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments

thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;

- Polesky, A.H. *et al.*, "Identification of Residues Critical for the Polymerase Activity of the Klenow Fragment of DNA Polymerase I from *Escherichia coli*," J. Biol. Chem. 265(24):14579-14591 (1990) describe site-directed mutagenesis of the putative active site of *E. coli* DNA polymerase I. Polesky *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Prasad, V.R. *et al.*, "Isolation and characterization of a dideoxyguanosine triphosphate-resistant mutant of human immunodeficiency virus reverse transcriptase," Proc. Natl. Acad. Sci. USA 88:11363-11367 (1991) describe the isolation and characterization of a drug-resistant mutant of HIV reverse transcriptase. Prasad *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Reha-Krantz, L.J. *et al.*, "Bacteriophage T4 DNA Polymerase Mutations That Confer Sensitivity to the PP_i Analog Phosphonoacetic Acid," J. Virology 67(1):60-66 (1993) describe the identification of mutations that confer sensitivity to the pyrophosphate analog phosphonoacetic acid in bacteriophage T4 DNA polymerase. Reha-Kranz *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Rhoades, M., "New Physical Map of Bacteriophage T5 DNA," J. Virology 43(2):566-573 (1982) describes the mapping of 103 cleavage sites produced by 13 restriction endonucleases on the DNA of bacteriophage T5. Rhoades *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Sawaya, M.R. *et al.*, "Crystal Structure of Rat DNA Polymerase β: Evidence for a Common Polymerase Mechanism," Science 264:1930-1935 (Jun. 1994)

describes the crystal structure of rat DNA polymerase β. Sawaya *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;

- Song, Q. *et al.*, "Mutagenesis of the Glu-89 Residue in Human Immuodeficiency Virus Type 1 (HIV-1) and HIV-2 Reverse Transcriptases: Effects on Nucleoside Analog Resistance," J. Virology 66(12):7568-7571 (1993) describe mutagenesis of the Glu-89 residue of HIV reverse transcriptases and their effect on resistance to inhibition by dideoxynucleoside analogs. Song *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Sousa, R. *et al.*, "Crystal structure of bacteriophage T7 RNA polymerase at 3.3 Angstrom resolution," Nature 364:593-599 (1993) describes the crystal structure of T7 DNA polymerase and discusses the identification of a cleft that can accommodate a double-stranded DNA template. Sousa *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Tabor, S. *et al.*, "*Escherichia coli* Thioredoxin Confers Processivity on the DNA Polymerase Activity of the Gene 5 Protein of Bacteriophage T7," J. Biol. Chem. 262(33):16212-16223 (1987) describe the purification of bacteriophage T7 gene 5 protein and the effect of thioredoxin on its processivity. Tabor *et al.* do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*;
- Tabor, S. and Richardson, C.C., "Effect of manganese ions on the incorporation of dideoxynucleotides by bacteriophage T7 DNA polymerase and *Escherichia coli* DNA polymerase I," Proc. Natl. Acad. Sci. USA 86:4076-4080 (1989) describe the effect of Mn2+ and Mg2+ on incorporation of dideoxynucleotides by T7 DNA polymerase. Tabor and Richardson do not describe a composition

comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*; and

- Tabor, S. and Richardson, C.C., "Selective Inactivation of the Exonuclease Activity of Bacteriophage T7 DNA Polymerase by in Vitro Mutagenesis," J. Biol. Chem. 264(11):6447-6458 (1989) describe the inactivation of bacteriophage T7 DNA polymerase gene 5 protein by reactive oxygen species. Tabor and Richardson do not describe a composition comprising a purified DNA polymerase, or fragments thereof, capable of DNA synthetic activity, said polymerase derived from *Thermotoga neapolitana*.

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